

Exhibit 3

Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment



WHAT'S KNOWN ON THIS SUBJECT: Puberty suppression has rapidly become part of the standard clinical management protocols for transgender adolescents. To date, there is only limited evidence for the long-term effectiveness of this approach after gender reassignment (cross-sex hormones and surgery).



WHAT THIS STUDY ADDS: In young adulthood, gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers. The clinical protocol including puberty suppression had provided these formerly gender-dysphoric youth the opportunity to develop into well-functioning young adults.

abstract

BACKGROUND: In recent years, puberty suppression by means of gonadotropin releasing hormone analogs has become accepted in clinical management of adolescents who have gender dysphoria (GD). The current study is the first longer term longitudinal evaluation of the effectiveness of this approach.

METHODS: A total of 55 young transgender adults (22 transwomen and 33 transmen) who had received puberty suppression during adolescence were assessed 3 times: before the start of puberty suppression (mean age, 13.6 years), when cross sex hormones were introduced (mean age, 16.7 years), and at least 1 year after gender reassignment surgery (mean age, 20.7 years). Psychological functioning (GD, body image, global functioning, depression, anxiety, emotional and behavioral problems) and objective (social and educational/professional functioning) and subjective (quality of life, satisfaction with life and happiness) well being were investigated.

RESULTS: After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved. Well being was similar to or better than same age young adults from the general population. Improvements in psychological functioning were positively correlated with postsurgical subjective well being.

CONCLUSIONS: A clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well functioning young adults. *Pediatrics* 2014;134:696–704

AUTHORS: Annelou L.C. de Vries, MD, PhD,^a Jenifer K. McGuire, PhD, MPH,^b Thomas D. Steensma, PhD,^a Eva C.F. Wagenaar, MD,^a Theo A.H. Doreleijers, MD, PhD,^a and Peggy T. Cohen-Kettenis, PhD^a

^aCenter of Expertise on Gender Dysphoria, VU University Medical Center, Amsterdam, Netherlands; and ^bDepartment of Human Development, Washington State University, Pullman, Washington

KEY WORDS

gender dysphoria, transgenderism, adolescents, psychological functioning, puberty suppression, longitudinal outcomes

ABBREVIATIONS

ABCL	Adult Behavior Checklist
ASR	Adult Self Report
BDI	Beck Depression Inventory
BIS	Body Image Scale
CBCL	Child Behavior Checklist
CGAS	Children's Global Assessment Scale
CSH	cross sex hormones
GD	gender dysphoria
GnRHa	gonadotropin releasing hormone analogs
GRS	gender reassignment surgery
SHS	Subjective Happiness Scale
STAI	Spielberger's Trait Anxiety Scale
SWLS	Satisfaction With Life Scale
TPI	Spielberger's Trait Anger Scale
UGDS	Utrecht Gender Dysphoria Scale
YSR	Youth Self Report

Dr de Vries conceptualized the study, clinically assessed the participants, drafted the initial manuscript, and reviewed and revised the manuscript; Dr McGuire conceptualized the study, planned and carried out the analyses, assisted in drafting the initial manuscript, and reviewed and revised the manuscript; Dr Steensma conceptualized the study, coordinated and supervised data collection, and reviewed and revised the manuscript; Dr Wagenaar coordinated and invited participants for assessments and reviewed and revised the manuscript; Drs Doreleijers and Cohen Kettenis conceptualized the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

Dr McGuire's current affiliation is Department of Family Social Science, College of Education and Human Development, St Paul, Minnesota.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-2958

doi:10.1542/peds.2013-2958

Accepted for publication Jul 7, 2014

Address correspondence to Annelou L.C. de Vries, MD, PhD, Child and Adolescent Psychiatrist, Center of Expertise on Gender Dysphoria, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, Netherlands. E mail: alc.devries@vumc.nl

(Continued on last page)

Transgender adolescents experience an incongruence between their assigned gender and their experienced gender and may meet the Diagnostic and Statistical Manual of Mental Disorders 5 criteria for gender dysphoria (GD).¹ Fifteen years ago, pubertal delay was introduced as an aid in the treatment of a gender dysphoric adolescent.² Although not without debate, blocking pubertal development has rapidly become more widely available^{3–7} and is now part of the clinical management guidelines for GD.^{8–12}

Gonadotropin releasing hormone analogs (GnRHAs) are a putatively fully reversible¹³ medical intervention intended to relieve distress that gender dysphoric adolescents experience when their secondary sex characteristics develop. A protocol designed by Cohen Kettenis and Delemarre van de Waal¹⁴ (sometimes referred to as “the Dutch model”)^{4,7} considers adolescents, after a comprehensive psychological evaluation with many sessions over a longer period of time, eligible for puberty suppression, cross sex hormones (CSH), and gender reassignment surgery (GRS) at the respective ages of 12, 16, and 18 years when there is a history of GD; no psychosocial problems interfering with assessment or treatment, for example, treatment might be postponed because of continuous moving from 1 institution to another or repeated psychiatric crises; adequate family or other support; and good comprehension of the impact of medical interventions.¹² Puberty suppression is only started after the adolescent actually enters the first stages of puberty (Tanner stages 2–3), because although in most prepubertal children GD will desist, onset of puberty serves as a critical diagnostic stage, because the likelihood that GD will persist into adulthood is much higher in adolescence than in the case of childhood GD.^{15,16}

Despite the apparent usefulness of puberty suppression, there is only limited evidence available about the effective-

ness of this approach. In the first cohort of adolescents who received GnRHAs, we demonstrated an improvement in several domains of psychological functioning after, on average, 2 years of puberty suppression while GD remained unchanged.¹⁶ The current study is a longer term evaluation of the same cohort, on average, 6 years after their initial presentation at the gender identity clinic. This time, we were not only interested in psychological functioning and GD, but added as important outcome measures objective and subjective well being (often referred to as “quality of life”), that is, the individuals’ social life circumstances and their perceptions of satisfaction with life and happiness.^{17–19} After all, treatment cannot be considered a success if GD resolves without young adults reporting they are healthy, content with their lives, and in a position to make a good start with their adult professional and personal lives.²⁰ Because various studies show that transgender youth may present with psychosocial problems,^{21,22} a clinical approach that includes both medical (puberty suppression) and mental health support (regular sessions, treatment when necessary, see Cohen Kettenis et al¹²) aims to improve long term well being in all respects.

In the present longitudinal study, 3 primary research questions are addressed. Do gender dysphoric youth improve over time with medical intervention consisting of GnRHAs, CSH, and GRS? After gender reassignment, how satisfied are young adults with their treatment and how do they evaluate their objective and subjective well being? Finally, do young people who report relatively greater gains in psychological functioning also report a higher subjective well being after gender reassignment?

METHODS

Participants and Procedure

Participants included 55 young adults (22 transwomen [natal males who

have a female gender identity] and 33 transmen [natal females who have a male gender identity]) of the first cohort of 70 adolescents who had GD who were prescribed puberty suppression at the Center of Expertise on Gender Dysphoria of the VU University Medical Center and continued with GRS between 2004 and 2011. These adolescents belonged to a group of 196 consecutively referred adolescents between 2000 and 2008, of whom 140 had been considered eligible for medical intervention and 111 were prescribed puberty suppression (see de Vries et al¹⁶). The young adults were invited between 2008 and 2012, when they were at least 1 year past their GRS (vaginoplasty for transwomen, mastectomy and hysterectomy with ovariectomy for transmen; many transmen chose not to undergo a phalloplasty or were on a long waiting list). Non participation ($n = 15$, 11 transwomen and 4 transmen) was attributable to not being 1 year postsurgical yet ($n = 6$), refusal ($n = 2$), failure to return questionnaires ($n = 2$), being medically not eligible (eg, uncontrolled diabetes, morbid obesity) for surgery ($n = 3$), dropping out of care ($n = 1$), and 1 transfemale died after her vaginoplasty owing to a postsurgical necrotizing fasciitis. Between the 55 participants and the 15 nonparticipating individuals, Student’s t tests revealed no significant differences on any of the pretreatment variables. A similar lack of differences was found between the 40 participants who had complete data and the 15 who were missing some data.

Participants were assessed 3 times: pre treatment (T0, at intake), during treatment (T1, at initiation of CSH), and post treatment (T2, 1 year after GRS). See Table 1 for age at the different time points. The VU University Medical Center medical ethics committee approved the study, and all participants gave informed consent.

TABLE 1 Age at Different Treatment Milestones and Intelligence by Gender

Variable	All Participants ^a (N = 55)	Transwomen (Natal Males) (N = 22)	Transmen (Natal Females) (N = 33)
Age, y	Mean (SD)	Range	Mean (SD)
At assessment PreT	13.6 (1.9)	11.1–17.0	13.6 (1.8)
At start of GnRHa	14.8 (1.8)	11.5–18.5	14.8 (2.0)
At start of CSH	16.7 (1.1)	13.9–19.0	16.5 (1.3)
At GRS	19.2 (0.9)	18.0–21.3	19.6 (0.9)
At assessment PostT	20.7 (1.0)	19.5–22.8	21.0 (1.1)
Full scale intelligence ^b	99.0 (14.3)	70–128	97.8 (14.2)

PostT, post treatment; PreT, pre treatment

^a Comparisons between those who had complete data (n = 40) and those who had missing data on the CBCL/ABCL (n = 15) reveal no significant differences between the groups in age at any point in the study or in natal sex.^b WISC R, the WISC III, or the WAIS III at first assessment, depending on age and time.^{45–47}

Measures

Time was the predominate independent variable. Other demographic characteristics were incorporated in some models, including, age, natal sex, Full Scale Intelligence, and parent marital status; where significantly different they are reported.

Gender Dysphoria/Body Image

There was 1 indicator measuring GD (Utrecht Gender Dysphoria Scale [UGDS]) and 3 indicators measuring body image (Body Image Scale [BIS] with primary, secondary, and neutral subscales). Higher UGDS (12 items, 1–5 range, total score ranging from 12–60) total scores indicate higher levels of GD, for example, "I feel a continuous desire to be treated as a man/woman."²³ There are separate versions of the UGDS for males and females with mostly different items, permitting no gender difference analyses. BIS (30 items, 1–5 range) higher scores indicate more dissatisfaction with primary sex characteristics (important gender defining body characteristics, eg, genitals, breasts), secondary sex characteristics (less obvious gender defining features, eg, hips, body hair), and neutral (hormonally unresponsive) body characteristics (eg, face, height).²⁴ The male and the female BIS are identical except for the sexual body parts. The UGDS and the BIS of the natal gender were administered at T0 and T1. At T1, we chose the UGDS of the assigned gender, because no physical changes had occurred yet and some were still

treated as their assigned gender. This way, however, decreased GD caused by social transitioning was not measured. At T2 young adults filled out the versions of their affirmed gender.

Psychological Functioning

There were 10 indicators assessing psychological functioning. To assess global functioning, the Children's Global Assessment Scale (CGAS) was used.²⁵ The Beck Depression Inventory (BDI; 21 items, 0–3 range) indicates presence and severity of depressive symptoms.²⁶ Spielberger's Trait Anger (TPI) and Spielberger's Trait Anxiety (STA; 10 and 20 items, respectively, 1–4 range) scales of the State Trait Personality Inventory were administered to assess the tendency to respond with anxiety or anger, respectively, to a threatening or annoying situation.^{27,28}

Behavioral and emotional problems were assessed by the total, internalizing, and externalizing T scores as well as clinical range scores for these 3 indices (T score >63) of the Child/Adult Behavior Checklist (CBCL at T0 and T1, ABCL at T2), the Youth/Adult Self Report (YSR at T0 and T1, ASR at T2).^{29–31} Items referring to GD in the CBCL/YSR and ABCL/ASR were scored as 0 (for more explanation, see Cohen Kettenis et al³²).

Objective and Subjective Well Being (T2 Only)

A self constructed questionnaire was used to ask the young adults about their current life circumstances, such

as living conditions, school and employment, and social support (objective well being), and satisfaction with treatment (subjective well being). Three instruments further assessed subjective well being. To measure quality of life, the WHOQOL-BREF (quality of life measure developed by the World Health Organization) was administered (24 items, 4 domains: Physical Health, Psychological Health, Social Relationships, and Environment, 1–5 range with higher scores indicating better quality of life).¹⁷ The Satisfaction With Life Scale (SWLS, 5 items, 5–35 range, 20 being neutral) was used to assess life satisfaction.¹⁸ Higher scores on the Subjective Happiness Scale (SHS, 4 items, 7 point Likert scale, average score 1–7) reflect greater happiness.¹⁹

Data Analyses

General Linear Models examined the repeated measures with an analysis of variance based model, incorporating continuous and categorical predictors, and correcting for the unbalanced cell sizes. Linear and quadratic effects of the 14 indicators across 3 time points, with time as the within subjects factor, and sex as a between subjects factor in a second set of analyses are reported in Tables 2 and 3 and Fig 1. A linear effect signifies an overall change across T0 to T2. A quadratic effect signifies that the change was not continuous, such as when an indicator does not improve from T0 to T1 but improves from T1 to T2. It is possible to have both a significant linear and quadratic effect on the same

TABLE 2 Gender Dysphoria and Body Image of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N ^a	T0	T1	T2	T0 T2		Time	Time × Sex		
					t test	Linear Effect				
		Mean (SD)	Mean (SD)	Mean (SD)	P	P				
UGDS	33	53.51 (8.29)	54.39 (7.70)	15.81 (2.78)	<.001					
MtF	11	47.07 (11.05)	48.95 (10.80)	17.27 (2.57)	<.001	<.001	<.001	n/a		
FtM	22	56.74 (3.74)	57.11 (3.40)	15.08 (2.64)	<.001	<.001	<.001	n/a		
Body Image (BIS)										
Primary sex characteristics	45	4.13 (0.59)	4.05 (0.60)	2.59 (0.82)	<.001	<.001	.01			
MtF	17	4.03 (0.68)	3.82 (0.56)	2.07 (0.74)	<.001	<.001	.45			
FtM	28	4.18 (0.53)	4.13 (0.60)	2.89 (0.71)	<.001					
Secondary sex characteristics	45	2.73 (0.72)	2.86 (0.67)	2.27 (0.56)	<.001	<.001	.10			
MtF	17	2.63 (0.60)	2.34 (0.68)	1.93 (0.63)	<.001					
FtM	28	2.80 (0.72)	3.18 (0.43)	2.48 (0.40)	.05					
Neutral body characteristics	45	2.35 (0.68)	2.49 (0.53)	2.23 (0.49)	.29	.29	.007			
MtF	17	2.57 (0.70)	2.29 (0.50)	2.09 (0.56)	.014	.01	.01			
FtM	28	2.21 (0.64)	2.61 (0.52)	2.32 (0.44)	.40					

MtM, female to male transgender; MtF, male to female transgender; n/a, not applicable

^a Participants who had complete data at all 3 waves were included. Some assessments were added to the study later, yielding fewer total participants for those scales.

indicator. Other potential between subjects factors (age, total IQ, parental marital status) were examined but excluded owing to a lack of relationship with the 14 indicators at T0. The 1 exception, age predicting secondary sex characteristics, is described below in the findings. We compared T2 sample means to population norms for subjective well-being using 1 sample *t* tests from previously published validation studies. Finally, we examined T2 subjective well-being correlations with residual change scores from T0 to T2 on the 14 indicators (an indicator of who improved relatively more or less over time).

All measures used were self reported, except the CGAS (attending clinician) and the CBCL/ASR (parents). Each participant was given all measures at each of 3 assessments. Numbers varied across indicators owing to the later inclusion of the YSR, CGAS, BDI, TPI, and STAI, yielding 8 persons who had missing data at T0 and a clinician error yielding missing data at T1 for 10 participants on the UGDS. Dutch versions were used (see de Vries et al¹⁶).

RESULTS

Gender Dysphoria and Body Satisfaction

Figure 1 and Table 2 show that GD and body image difficulties persisted through puberty suppression (at T0 and T1) and remitted after the administration of CSH and GRS (at T2) (significant linear effects in 3 of 4 indicators, and significant quadratic effects in all indicators). Time by sex interactions revealed that transwomen reported more satisfaction over time with primary sex characteristics than transmen and a continuous improvement in satisfaction with secondary and neutral sex characteristics. Transmen reported more dissatisfaction with secondary and neutral sex characteristics at T1 than T0, but improvement in both from T1 to T2. Age was a significant covariate with secondary sex characteristics (the only significant demographic covariate with any outcome indicator in the study), indicating that older individuals were more dissatisfied at T0, but the age gap in body satisfaction narrowed over time ($F(1, 42) = 8.18; P < .01$).

Psychological Functioning

As presented in Table 3, significant linear effects showed improvement over time in global functioning (CGAS), CBCL/ABCL total, internalizing and externalizing *T* scores, and YSR/ASR total and internalizing *T* scores. Quadratic effects revealed decreases from T0 to T1 followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. Quadratic trends revealed decreases from T0 to T1, followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. For all CBCL/ABCL and YSR/ASR indicators except YSR/ASR externalizing, the percentage in the clinical range dropped significantly (McNemar's test, *P* value <0.05) from T0 to T1, from T0 to T2, or from T1 to T2.

Over time, transmen showed reduced anger, anxiety, and CBCL/ABCL externalizing *T* scores, whereas transwomen showed stable or slightly more symptomatology on these measures. Trans women improved in CBCL/ABCL total *T* scores in a quadratic fashion (all the improvement between T1 and T2),

TABLE 3 Psychological Functioning of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N ^a	T0	T1	T2	T0 T2	Time		Time × Sex		
						t test	Linear Effect		Quadratic Effect	
							P	P	P	P
Global functioning (CGAS)	32	71.13 (10.46)	74.81 (9.86)	79.94 (11.56)	<.001		<.001	.89		.68
MtF	15	74.33 (7.53)	78.20 (9.56)	82.40 (8.28)	<.001		.61			
FtM	17	67.65 (11.87)	70.65 (9.89)	76.29 (14.48)	.02					
Depression (BDI)	32	7.89 (7.52)	4.10 (6.17)	5.44 (8.40)	.21		.23	.66		.49
MtF	12	4.73 (4.20)	2.25 (3.54)	3.38 (4.40)	.12					
FtM	20	10.09 (8.34)	5.05 (7.08)	6.95 (9.83)	.32					
Anger (TPI)	32	17.55 (5.72)	17.22 (5.61)	16.01 (5.28)	.20		.15	.04		.12
MtF	12	14.17 (3.01)	14.00 (3.36)	5.58 (3.92)	.18					
FtM	20	19.55 (5.96)	19.25 (5.69)	16.56 (6.06)	.05					
Anxiety (STAI)	32	39.57 (10.53)	37.52 (9.87)	37.61 (10.39)	.45		.42	.05		.52
MtF	12	31.87 (7.42)	31.71 (8.36)	35.83 (10.22)	.14					
FtM	20	44.41 (9.06)	41.59 (9.03)	39.20 (10.53)	.12					
CBCL ABCL										
Total T score	40	60.20 (12.66)	54.70 (11.58)	48.10 (9.30)	<.001		<.001	.25		
% Clinical		38 _x	20 _y	5 _y			.68	.03		
MtF	15	57.40 (12.76)	49.67 (12.29)	48.13 (12.58)	.002					
FtM	25	61.88 (12.56)	57.72 (10.23)	48.08 (6.95)	<.001					
Int T score	40	60.83 (12.36)	54.42 (10.58)	50.45 (10.04)	<.001		<.001	.91		
% Clinical		30 _x	12.5 _y	10 _y			.42	.33		
MtF	15	59.40 (10.03)	50.93 (11.15)	48.73 (12.61)	<.001					
FtM	25	61.68 (13.70)	56.52 (9.86)	51.48 (8.25)	<.001					
Ext T score	40	57.85 (13.73)	53.85 (12.77)	47.85 (8.59)	<.001		<.001	.19		
% Clinical		40 _x	25 _x	2.5 _y			.43	.12		
MtF	15	52.53 (14.11)	47.87 (12.07)	46.33 (10.95)	.10					
FtM	25	61.04 (12.71)	57.44 (12.01)	48.76 (6.89)	<.001					
YSR ASR										
Total T score	43	54.72 (12.08)	49.16 (11.16)	48.53 (9.46)	.005		.005	.28		
% Clinical		30 _x	14 _{xy}	7 _y			.07	.75		
MtF	17	50.65 (12.19)	45.94 (12.24)	47.24 (12.28)	.28					
FtM	26	57.38 (11.47)	51.27 (10.08)	49.38 (7.21)	.01					
Int T score	43	55.47 (13.08)	48.65 (12.33)	50.07 (11.15)	.03		.03	.87		
% Clinical		30 _x	9.3 _y	11.6 _{xy}			.008	.73		
MtF	17	54.00 (12.31)	47.59 (14.26)	48.12 (12.54)	.04					
FtM	26	56.42 (13.86)	49.35 (11.13)	51.35 (10.19)	.17					
Ext T score	43	52.77 (12.47)	49.44 (9.59)	49.44 (9.37)	.14		.14	.005		
% Clinical		21 _x	11.6 _x	7 _x			.09	.14		
MtF	17	46.00 (11.58)	44.71 (9.53)	50.24 (11.18)	.17					
FtM	26	57.16 (11.14)	52.54 (8.43)	48.92 (8.18)	.006					

FtM, female to male transgender; MtF, male to female transgender

^aPercent clinical range, shared subscripts indicate no significant difference in values. In no case was an increase in percent in the clinical range significant from 1 time point to any other time point, indicating an overall decline or stability of clinical symptoms over time^aParticipants who had complete data at all 3 waves were included. Some assessments were added to the study later, yielding fewer total participants for those scales

whereas transmen improved steadily across the 3 time points (linear effect only).

Objective Well Being

At T2, the participants were vocationally similar to the Dutch population except they were slightly more likely to live with parents (67% vs 63%), and more likely,

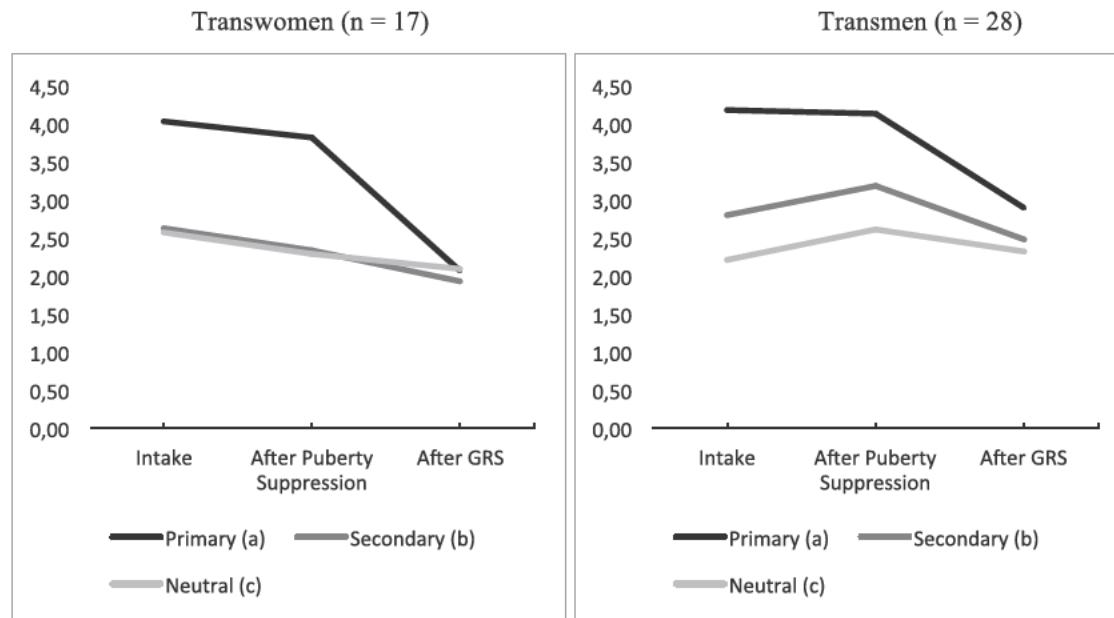
when studying, to be pursuing higher education (58% vs 31%).³³

Families were supportive of the transitioning process: 95% of mothers, 80% of fathers, and 87% of siblings. Most (79%) young adults reported having 3 or more friends, were satisfied with their male (82%) and female peers (88%), and almost all (95%) had received support

from friends regarding their gender reassignment. After their GRS, many participants (89%) reported having been never or seldom called names or harassed. The majority (71%) had experienced social transitioning as easy.

Subjective Well Being

None of the participants reported regret during puberty suppression, CSH



Eta Squared for Linear and Quadratic Effects

- (a) Primary sex characteristics
 - Time: .79 ($P < .001$), .66 ($P < .001$),
 - Time \times sex: .14 ($P = .01$), .01 ($P = .45$),
- (b) Secondary sex characteristics
 - Time: .31 ($P < .001$), .30 ($P < .001$),
 - Time \times sex: .06 ($P = .10$), .22 ($P < .001$)
- (c) Neutral body characteristics
 - Time: .07 ($P < .001$), .09 ($P = .29$)
 - Time \times sex: .16 ($P = .007$), .15 ($P = .01$)

FIGURE 1

BIS²³ for transwomen and transmen at T0 (pretreatment, at intake), T1 (during treatment, at initiation of cross gender hormones), and T2 (post treatment, 1 year after GRS).

treatment, or after GRS. Satisfaction with appearance in the new gender was high, and at T2 no one reported being treated by others as someone of their assigned gender. All young adults reported they were very or fairly satisfied with their surgeries.

Mean scores on WHOQOL BREF, the SWLS, and the SHS are presented in Table 4, together with scores from large validation and reliability studies of these measures,^{17,19,34} revealing similar scores in all areas except WHOQOL Environment subdomain, which was higher for the participants than the norm. There were some differences across gender; transwomen scored higher than transmen on the SWLS (mean = 27.7; SD = 5.0 vs mean = 23.2; SD = 6.0; $t(52)$

= 2.82; $P < .01$) and on the psychological subdomain of the WHOQOL (mean = 15.77; SD = 2.0 vs mean = 13.92; SD = 2.5; $t(53) = 2.95$; $P < .01$).

Correlations With Residual Change Scores

The residual change scores of secondary sex characteristics, global functioning, depression, anger, anxiety, and YSR total, internalizing and externalizing from T0 to T2, were significantly correlated with the 6 T2 quality of life indicators. Most correlation coefficients were within the moderate to large magnitude (eg, 0.30–0.60), except depression, which was highly correlated (0.60–0.80) (see Table 5).

DISCUSSION

Results of this first long term evaluation of puberty suppression among transgender adolescents after CSH treatment and GRS indicate that not only was GD resolved, but well-being was in many respects comparable to peers.

The effectiveness of CSH and GRS for the treatment of GD in adolescents is in line with findings in adult transsexuals.^{35,36} Whereas some studies show that poor surgical results are a determinant of postoperative psychopathology and of dissatisfaction and regret,^{37,38} all young adults in this study were generally satisfied with their physical appearance and none regretted treatment. Puberty suppression had caused their bodies to

TABLE 4 Subjective Well Being: Quality of Life, Satisfaction With Life, and Subjective Happiness Mean Scores With Scores From Validation Studies

	N	Mean (SD)	Range	Validation Studies Scores Mean (SD)	Comparison P
WHOQOL ^a Physical	55	15.22 (2.49)	8.6–20.0	15.0 (2.9) ^b	.56
WHOQOL Psychological	55	14.66 (2.44)	6.67–20.0	14.3 (2.8) ^b	.24
WHOQOL Social Relations	55	14.91 (2.35)	9.3–20.00	14.5 (3.4) ^b	.18
WHOQOL Environment	55	15.47 (2.06)	10.5–20.00	13.7 (2.6) ^b	<.001
SWLS	54	24.98 (6.0)	9.0–35.0	26.18 (5.7) ^c	.16
SHS	54	4.73 (0.77)	2.75–6.0	4.89 (1.1) ^d	.17

^a WHOQOL, Brief, Skevington et al¹⁶^b International field trial, ages 21 to 30 years, Skevington et al¹⁶^c Dutch young adults, Arindell et al³⁵^d US Public College Students, Lyubomirsky¹⁸

not (further) develop contrary to their experienced gender.

Psychological functioning improved steadily over time, resulting in rates of clinical problems that are indistinguishable from general population samples (eg, percent in the clinical range dropped from 30% to 7% on the YSR/ASR³⁰) and quality of life, satisfaction with life, and subjective happiness comparable to same age peers.^{17,19,34} Apparently the clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons gave these formerly gender dysphoric youth the opportunity to develop into well functioning young adults. These individuals, of whom an even higher percentage than the general population were pursuing higher education, seem different from the

transgender youth in community samples with high rates of mental health disorders, suicidality and self harming behavior, and poor access to health services.^{21,22,39,40}

In this study, young adults who experienced relatively greater improvements in psychological functioning were more likely to also report higher levels of subjective postsurgical well being. This finding suggests value to the protocol that involves monitoring the adolescents' functioning, physically and psychologically, over many years, and providing more support whenever necessary.

This clinic referred sample perceived the Environmental subdomain (with items like "access to health and social care" and "physical safety and secu-

rity") of the WHOQOL BREF as even better than the Dutch standardization sample.¹⁷ Whereas in some other contexts transgender youth may experience gender related abuse and victimization,^{22,41,42} the positive results may also be attributable to supportive parents, open minded peers, and the social and financial support (treatment is covered by health insurance) that gender dysphoric individuals can receive in the Netherlands.

Both genders benefitted from the clinical approach, although transwomen showed more improvement in body image satisfaction (secondary sex characteristics) and in psychological functioning (anger and anxiety). None of the transmen in this study had yet had a phalloplasty because of waiting lists or

TABLE 5 Correlations Between Residual Change in Psychological Functioning Over Time and Young Adult Subjective Well Being

	WHOQOL BREF					SHS
	Physical	Psychological	Social	Environment	SWLS	
Gender dysphoria (UGDS)	0.01 (.97)	0.05 (.75)	-0.09 (.57)	-0.02 (.89)	0.06 (.71)	0.30 (.04)
Body image subscales (BIS)						
Primary sex characteristics	-0.22 (.14)	-0.25 (.09)	-0.35 (.02)	-0.04 (.78)	-0.22 (.14)	-0.21 (.17)
Secondary sex characteristics	-0.39 (.006)	-0.45 (<.001)	-0.47 (<.001)	-0.34 (.02)	-0.35 (.02)	-0.26 (.08)
Neutral body characteristics	-0.21 (.16)	-0.27 (.07)	-0.15 (.32)	-0.28 (.06)	-0.26 (.08)	-0.16 (.28)
Psychological functioning						
Global functioning (CGAS)	0.60 (<.001)	0.52 (.002)	0.52 (.002)	0.27 (.14)	0.58 (<.001)	0.50 (.004)
Depression (BDI)	-0.76 (<.001)	-0.72 (<.001)	-0.51 (.002)	-0.49 (.003)	-0.61 (<.001)	-0.77 (<.001)
Trait anger (TPI)	-0.37 (.03)	-0.18 (.31)	-0.22 (.20)	-0.29 (.09)	-0.33 (.07)	-0.35 (.05)
Trait anxiety (STA)	-0.58 (<.001)	-0.64 (<.001)	-0.38 (.03)	-0.44 (.01)	-0.49 (.004)	-0.57 (<.001)
CBCL ABCL						
Total T score	-0.20 (.20)	-0.12 (.45)	-0.07 (.65)	-0.14 (.35)	-0.32 (.03)	-0.16 (.29)
Internalizing T score	-0.29 (.06)	-0.29 (.06)	-0.23 (.14)	-0.12 (.44)	-0.48 (<.001)	-0.36 (.02)
Externalizing T score	-0.13 (.40)	-0.05 (.75)	0.16 (.29)	-0.20 (.19)	-0.15 (.36)	0.00 (.99)
Youth Self Report (YSR ASR)						
Total T score	-0.53 (<.001)	-0.45 (.002)	-0.33 (.03)	-0.42 (.005)	-0.52 (<.001)	-0.55 (<.001)
Internalizing T score	-0.62 (<.001)	-0.61 (<.001)	-0.47 (<.001)	-0.40 (.007)	-0.66 (<.001)	-0.60 (<.001)
Externalizing T score	-0.23 (.13)	-0.10 (.53)	-0.07 (.67)	-0.37 (.02)	-0.22 (.15)	-0.35 (.02)

P values are in parentheses

a desire for improved surgery techniques. This finding warrants further study of the specific concerns of young transmen.

Despite promising findings, there were various limitations. First, the study sample was small and came from only 1 clinic. Second, this study did not focus on physical side effects of treatment. Publications on physical parameters of the same cohort of adolescents are submitted or in preparation. A concurring finding exists in the 22 year follow up of the well functioning first case now at age 35 years who has no clinical signs of a negative impact of earlier puberty suppression on brain development, metabolic and endocrine parameters, or bone mineral density.⁴³ Third, despite the absence of pretreatment differences on measured indicators, a selection bias could exist between adolescents of the original cohort that participated in this study compared with nonparticipants.

Age criteria for puberty suppression and CSH are under debate, although they worked well for adolescents in the current study. Especially in natal females, puberty will often start before the age of 12 years. Despite the fact that developing evidence suggests that cognitive and affective cross gender identification, social role transition, and age at assessment are related to persistence of childhood GD into adolescence, predicting individual persistence at a young age will always remain difficult.⁴⁴ The age criterion of 16 years for the start of CSH may be problematic especially for transwomen, as growth in height continues as long as cross sex steroids are not provided (causing the growth plates to close). Therefore, psychological maturity and the capacity to give full informed consent may surface as the required criteria for puberty suppression and CSH⁴⁵ in cases that meet other eligibility criteria.

CONCLUSIONS

Results of this study provide first evidence that, after CSH and GRS, a treatment protocol including puberty suppression leads to improved psychological functioning of transgender adolescents. While enabling them to make important age appropriate developmental transitions, it contributes to a satisfactory objective and subjective well being in young adulthood. Clinicians should realize that it is not only early medical intervention that determines this success, but also a comprehensive multidisciplinary approach that attends to the adolescents' GD as well as their further well being and a supportive environment.

ACKNOWLEDGMENTS

The authors thank the young adults and their parents for their repeated participation in this study over the years.

REFERENCES

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013
- Cohen Kettenis PT, van Goozen SH. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *Eur Child Adolesc Psychiatry*. 1998;7(4):246-248
- Nakatsuka M. [Adolescents with gender identity disorder: reconsideration of the age limits for endocrine treatment and surgery.] *Seishin Shinkeigaku Zasshi*. 2012; 114(6):647-653
- Zucker KJ, Bradley SJ, Owen Anderson A, Singh D, Blanchard R, Bain J. Puberty blocking hormonal therapy for adolescents with gender identity disorder: a descriptive clinical study. *J Gay Lesbian Ment Health*. 2010;15(1):58-82
- Hewitt JK, Paul C, Kasiannan P, Grover SR, Newman LK, Warne GL. Hormone treatment of gender identity disorder in a cohort of children and adolescents. *Med J Aust*. 2012; 196(9):578-581
- Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med*. 2011;165(2):171-176
- Spack NP, Edwards Leeper L, Feldman HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012;129(3): 418-425
- Byne W, Bradley SJ, Coleman E, et al. Treatment of gender identity disorder. *Am J Psychiatry*. 2012;169(8):875-876
- Adelson SL. Practice parameter on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2012;51(9): 957-974
- Hembree WC, Cohen Kettenis P, Delemarre van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;194(9):3132-3154
- Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender nonconforming people, version 7. *Int J Transgenderism*. 2012;13(4): 165-232
- Cohen Kettenis PT, Steensma TD, de Vries AL. Treatment of adolescents with gender dysphoria in the Netherlands. *Child Adolesc Psychiatr Clin N Am*. 2011;20(4):689-700
- Thornton P, Silverman LA, Geffner ME, Neely EK, Gould E, Danoff TM. Review of outcomes after cessation of gonadotropin releasing hormone agonist treatment of girls with precocious puberty. *Pediatr Endocrinol Rev Mar*. 2014;11(3):306-317
- Delemarre van de Waal HA, Cohen Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol*. 2006;155(suppl 1):S131-S137
- Steensma TD, Biemond R, Boer FD, Cohen Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow up study. *Clin Child Psychol Psychiatry*. 2011;16(4):499-516
- de Vries AL, Steensma TD, Doreleijers TA, Cohen Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow up study. *J Sex Med*. 2011;8(8):2276-2283
- Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL BREF

- quality of life assessment: psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual Life Res.* 2004;13(2): 299–310
18. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. *J Pers Assess.* 1985;49(1):71–75
 19. Lyubomirsky S, Lepper HS. A measure of subjective happiness: preliminary reliability and construct validation. *Soc Indic Res.* 1999;46(2):137–155
 20. Koot HM. The study of quality of life: concepts and methods. In: Koot HM, Wallander JL, eds. *Quality of Life in Child and Adolescent Illness: Concepts, Methods and Findings*. London, UK: Harwood Academic Publishers; 2001:3–20
 21. Carver PR, Yunger JL, Perry DG. Gender identity and adjustment in middle childhood. *Sex Roles.* 2003;49(3–4):95–109
 22. Grossman AH, D'Augelli AR. Transgender youth: invisible and vulnerable. *J Homosex.* 2006;51(1):111–128
 23. Steensma TD, Kreukels BP, Jurgensen M, Thyen U, De Vries AL, Cohen Kettenis PT. The Utrecht Gender Dysphoria Scale: a validation study. *Arch Sex Behav.* provisionally accepted
 24. Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav.* 1975;4:639–656
 25. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry.* 1983;40(11): 1228–1231
 26. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory II*. San Antonio, TX: Psychological Corporation; 1996
 27. Spielberger CD. *Manual for the State Trait Anger Expression Inventory (STAXI)*. Odessa, FL: Psychological Assessment Resources; 1988
 28. Spielberger CD, Gorssuch RL, Lushene PR, Vagg PR, Jacobs GA. *Manual for the State Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press, Inc; 1983
 29. Achenbach TM. *Manual for the Youth Self Report*. Burlington, VT: University of Vermont, Department of Psychiatry; 1991
 30. Achenbach TM, Rescorla LA. *Manual for the ASEBA Adult Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2003
 31. Achenbach TM, Edelbrock CS. *Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. Burlington, VT: University of Vermont, Department of Psychiatry; 1983
 32. Cohen Kettenis PT, Owen A, Kajiser VG, Bradley SJ, Zucker KJ. Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: a cross national, cross clinic comparative analysis. *J Abnorm Child Psychol.* 2003;31(1):41–53
 33. Statistics Netherlands. Landelijke Jeugdmonitor. In: Ministerie van Volksgezondheid, Wetenschap en Sport, ed. Den Haag, Heerlen: Tuijtel, Hardinxveld Giessendam; 2012
 34. Arrindell WA, Heesink J, Feij JA. The Satisfaction With Life Scale (SWLS): appraisal with 1700 healthy young adults in The Netherlands. *Pers Individ Dif.* 1999;26(5): 815–826
 35. Murad MH, Elamin MB, Garcia MZ, et al. Hormonal therapy and sex reassignment: a systematic review and meta analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf).* 2010;72(2):214–231
 36. Smith YL, Van Goozen SH, Kuiper AJ, Cohen Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med.* 2005; 35(1):89–99
 37. Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow up of fourteen male to female patients. *Arch Sex Behav.* 1989;18(2):145–153
 38. Lawrence AA. Factors associated with satisfaction or regret following male to female sex reassignment surgery. *Arch Sex Behav.* 2003;32(4):299–315
 39. Grossman AH, D'Augelli AR. Transgender youth and life threatening behaviors. *Suicide Life Threat Behav.* 2007;37(5):527–537
 40. Garofalo R, DeLeon J, Osmer E, Doll M, Harper GW. Overlooked, misunderstood and at risk: exploring the lives and HIV risk of ethnic minority male to female transgender youth. *J Adolesc Health.* 2006;38(3): 230–236
 41. Toomey RB, Ryan C, Diaz RM, Card NA, Russell ST. Gender nonconforming lesbian, gay, bisexual, and transgender youth: school victimization and young adult psychosocial adjustment. *Dev Psychol.* 2010;46(6):1580–1589
 42. McGuire JK, Anderson CR, Toomey RB, Russell ST. School climate for transgender youth: a mixed method investigation of student experiences and school responses. *J Youth Adolesc.* 2010;39(10): 1175–1188
 43. Cohen Kettenis PT, Schagen SE, Steensma TD, de Vries AL, Delemarre van de Waal HA. Puberty suppression in a gender dysphoric adolescent: a 22 year follow up. *Arch Sex Behav.* 2011;40(4):843–847
 44. Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow up study. *J Am Acad Child Adolesc Psychiatry.* 2013;52(6):582–590
 45. Kreukels BP, Cohen Kettenis PT. Puberty suppression in gender identity disorder: the Amsterdam experience. *Nat Rev Endocrinol.* 2011;7(8):466–472
 46. Wechsler D. *Wechsler Intelligence Scale for Children: Manual*. 3rd ed. San Antonio, TX: The Psychological Corporation; 1997
 47. Wechsler D. *Wechsler Adult Intelligence Scale (WAIS III)*. 3rd ed. Dutch version. Lisse, Netherlands: Swets and Zetlinger; 1997
 48. Wechsler D, Kort W, Compaan EL, Bleichrodt N, Resing WCM, Schittkatte M. *Wechsler Intelligence Scale for Children (WISC III)*. 3rd ed. Lisse, Netherlands: Swets and Zetlinger; 2002

(Continued from first page)

PEDIATRICS (ISSN Numbers: Print, 0031 4005; Online, 1098 4275).

Copyright © 2014 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by a personal grant awarded to the first author by the Netherlands Organization for Health Research and Development (ZonMw 100002028).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.